PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 21085.0067P1	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/037394	International filing date *(day/month/year)* 10 November 2004 (10.11.2004)	Priority date *(day/month/year)* 10 November 2003 (10.11.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant UAB RESEARCH FOUNDATION		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 15 May 2006 (15.05.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Authorized officer Philippe Becamel Telephone No. +41 22 338 70 90

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/037394	International filing date *(day/month/year)* 10.11.2004
Priority date *(day/month/year)* 10.11.2003	
International Patent Classification (IPC) or both national classification and IPC A61K39/09, C12N9/24, A61P11/02, C07K16/12	
Applicant UAB RESEARCH FOUNDATION	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Page, M Telephone No. +49 89 2399-7322

Form (PCT/ISA/237) (Cover Sheet) (January 2004)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/037394

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☒ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 27-45, 53-125

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 27-45, 53-125

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-26,46-52

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	24,26,50,52
	No:	Claims	1-23,25,46-49,51
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-26,46-52
Industrial applicability (IA)	Yes:	Claims	20-26,46-52: Opinion reserved.
	No:	Claims	

2. Citations and explanations

   see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

   and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

   see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The application concerns the provision of pneumococcal neuraminidase for vaccination purposes.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The Applicant has elected not to pay additional search fees for inventions 2-8 as outlined in the Search Report. No examination is possible for unsearched subject matter, i.e. **claims 27-45 and 53-125**.

Re Item IV

Lack of Unity of Invention

The application centres on the use of certain antigens giving immune protection against pneumococcal infection. Four distinct antigens are claimed as well as antibodies against two of these moieties, the antigens being pneumococcal neuraminidase, detoxified neuraminidase, phosphocholine teichoic acid and non-phosphocholine teichoic acid. The various combinations given in the application lead to the Examiner's finding of eight partially overlapping inventive concepts.

Apart from antigenic fragments of pneumococcal neuraminidase and their potential therapeutic benefit being well known in the art (see for example WO 02/077021, WO 02/083855, US 6699703), Briles *et al.* 1981 (cited in the application) detail the efficacy of anti-phosphocholine antibodies in preventing *Streptococcus pneumoniae* infection in mice, a disclosure which corresponds to the product and method of claims 113 and 122. In light of Briles *et al.*, these concepts lack an special technical feature conferring unity of invention on the whole application.

The eight partially overlapping concepts are:

Invention I **Claims 1-26 and 46-52**

The application concerns the provision of pneumococcal neuraminidase for vaccination purposes.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The Applicant has elected not to pay additional search fees for inventions 2-8 as outlined in the Search Report. No examination is possible for unsearched subject matter, i.e. **claims 27-45 and 53-125**.

Re Item IV

Lack of Unity of Invention

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The eight partially overlapping concepts are:

Invention I Claims 1-26 and 46-52

A detoxified pneumococcal neuraminidase or an antigenic portion thereof, composition comprising the same and method of treatment using the same.

Invention II Claims 27-32,38-45

Method of treatment using pneumococcal neuraminidase or an antigenic fragment thereof, a composition comprising the same and containers comprising said composition.

Invention III Claims 33-37

Method of treatment using pneumococcal neuraminidase antibody or a fragment thereof.

Invention IV Claims 53-67

A composition comprising a phosphocholine or an antigenic portion thereof of pneumococcal teichoic acid or lipoteichoic acid, containers comprising said composition and method of treatment using the same.

Invention V Claims 68-82

A composition comprising pneumococcal neuraminidase or an antigenic portion thereof and a phosphocholine or an antigenic portion thereof of pneumococcal teichoic acid or lipoteichoic acid, containers comprising said composition and method of treatment comprising the same.

Invention VI Claims 83-97

A composition comprising a non-phosphocholine antigenic portion of pneumococcal teichoic acid or lipoteichoic acid, containers comprising said composition and method of treatment using the same.

Invention VII Claims 98-112

A composition comprising pnuemococcal neuraminidase or an antigenic portion thereof and a non-phosphocholine antigenic portion of pneumococcal teichoic acid or lipoteichoic acid, containers comprising said composition and method of treatment using the same.

Invention VIII Claims 113-125

A composition comprising a phosphocholine antibody or a fragment thereof, containers comprising said composition and method of treatment using the same.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 Reference is made to the following documents:

D1: CAMARA M ET AL: "A NEURAMINIDASE FROM STREPTOCOCCUS PNEUMONIAE HAS THE FEATURES OF A SURFACE PROTEIN" INFECTION AND IMMUNITY, AMERICAN SOCIETY OF MICROBIOLOGY, WASHINGTON, DC, US, vol. 62, no. 9, September 1994 (1994-09), pages 3688-3695, XP001118871 ISSN: 0019-9567

D2: HOSKINS J ET AL: "Genome of the Bacterium Streptococcus pneumoniae Strain R6" JOURNAL OF BACTERIOLOGY, WASHINGTON, DC, US, vol. 183, no. 19, October 2001 (2001-10), pages 5709-5717, XP002231307 ISSN: 0021-9193

D3: WO 02/077021 A (CHIRON SPA; THE INSTITUTE FOR GENOMIC RESEARCH; MASIGNANI, VEGA; TETTE) 3 October 2002 (2002-10-03)

D4: WO 02/083855 A (AMERICAN CYANAMID COMPANY; ZAGURSKY, ROBERT, JOHN; MASI, AMY, WADHAMS;) 24 October 2002 (2002-10-24)

D5: BRILES D E ET AL: "MOUSE IMMUNO GLOBULIN G-3 ANTIBODIES ARE HIGHLY PROTECTIVE AGAINST INFECTION WITH STREPTOCOCCUS-PNEUMONIAE" NATURE (LONDON), vol. 294, no. 5836, 1981, pages 88-90, XP002326578 ISSN: 0028-0836

D6: MARTINOT A ET AL: "HEMOLYTIC-UREMIC SYNDROME ASSOCIATED WITH STREPTOCOCCUS-PNEUMONIAE MENINGITIS" EUROPEAN JOURNAL OF PEDIATRICS, vol. 148, no. 7, 1989, pages 648-649, XP002326579 ISSN: 0340-6199

V.2 Novelty - Art.33(1) and (2) PCT:

1. There is nothing in **claim 1** and subsequent claims to specify that the antigenic portion of the neuraminidase is any different from fragments already known in the art. An antigenic portion of a detoxified neuraminidase can be identical to an antigenic portion of a native neuramindase as the claims do not specify that the antigenic portion

comprises the change resulting in the desired detoxification. D3 and D4 both disclose fragments of *S. pneumoniae* neuraminidase for vaccination purposes, with D4 specifically suggesting nasal application. The sole feature of the claims not to be found in D3 or D4 is a reference to haemolytic uremia (claims 26 and 52). All other claims are anticipated.

V.3 Inventive Step - Art.33(1) and (3) PCT:

1. The application is based on the speculation that partially inactivated pneumococcal neuraminidase will form a suitable antigen for protection against pneumoccal infection. A number of specific modifications to the polyeptide are put forward, but the application does not disclose any partially inactivated neuraminidases, nor does it disclose antigens that have been shown to have a protective effect, whether systemically or nasally applied.

2. Starting from D3 or D4 as the closest prior art (both documents disclose multiple potential *P. streptococcus* antigens including neuraminidases and fragments thereof, not to mention nasal application techniques), it cannot be seen what teaching is brought to the art by the present application and inventive step cannot be acknowledged. Even if the Applicant were to restrict the subject matter to specific embodiments as defined in the claims it would still not be possible to acknowledge inventive step in the absence of any evidence that the technical problem, namely the prevention of pneumococcal infection, has been solved.

V.4 Industrial Applicability - Art.33(1) and (4) PCT:

1. No unified criteria exist in the PCT Contracting States on the question whether methods of treatment are industrially applicable, as they are not considered to be industrially applicable in the EPC. No opinion can be given, therefore on the industrial applicability of **claims 20-26 and 46-52**, which claim such methods.

V.5 Requirements for any Amendments Art. 34(2)(b) PCT:

1. Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.

2. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

Re Item VIII
Certain observations on the international observation

1. **Claims 1-26 and 46-52** attempt to distinguish the subject matter from that which is known in the prior art by defining the neuraminidase as having been detoxified. This is considered to constitute a functional definition and not a technical or structural one and therefore to be unclear (Article 6 PCT). Even though the application discusses several ways in which a neuraminidase can be detoxified (or, to be more precise, partially inactivated), the claims should define the subject matter for which protection is sought in terms of concrete technical features.

2. Furthermore, the definition rendered in the description to this term leads to a conflict between the generally accepted meaning of the word detoxified and what the Applicant wishes to convey according to page 15 and following, where a detoxified neuraminidase is defined as being a neuraminidase that exhibits decreased activity as compared to non-detoxified enzyme. Although it is appreciated that pneumococcal neuraminidase contributes to the pathology of pneumococcal infection, the enzyme per se is not technically toxic and cannot be detoxified. Even if this was the case, then the absolute "detoxified" (no longer toxic) is at odds with the Applicant's desired definition of being a little less toxic. In order to bring the claims into conformity with Article 6 PCT, the term

should be corrected and defined, e.g. through incorporation of the definition in the passage spanning pages 15 and 16.

3. **Claims 14-17** are meaningless without an adequate definition of what constitutes the C-terminus of the claimed neuraminidase. Merely stating that it corresponds to residue 800 of a given neuraminidase without instructing the skilled practitioner what is meant by "corresponds to" or how to align the sequences is considered to result in the said claims lacking clarity (Article 6 PCT).

4. Lastly, the application is not considered to be adequately disclosed or supported, as none of the Examples demonstrate any specific effect of detoxified neuraminidase in comparison to wild type enzymes, nor does it disclose a specific detoxified neuraminidase (Article 5 PCT).